

## **REMARKS**

This Amendment is presented in response to the Office Action dated June 11, 2010, along with a request for an extension of time.

### **Status of Claims**

Claims 38, 39, 43-55, 57-58, 60-65, and 68 – 74 are now pending in this application. Claims 40-43, 56, 59, 66 and 67 have been cancelled and new claims 68-74 have been added. No fees are due for the addition of claims, as 8 claims were canceled and 8 claims were added. There are two independent claims, claims 38 and 69. Support for new claims 68-72 is found directly from the original claims, namely, claims 2, 10 and 22-27, and paragraph [101] of the specification. Support for new claim 73 is found in Table 1, page 38 of the specification. Support for new claim 74 is found in paragraph [0032] of the specification.

Claim 38 has been amended for the purpose of expediting prosecution. In particular, claim 38 has now been amended such that the active ingredient in the unit dose is “a therapeutically effective amount of an active agent(s) **comprising tizanidine or a pharmaceutically acceptable salt thereof** incorporated into an immediate release pharmaceutically acceptable excipient.” This change is made in order to expedite prosecution only and is made without prejudice to Applicant pursuing broader or different claims in the future, and is made not as an admission or narrowing of the claimed subject matter in view of the Examiner’s rejection under 35 U.S.C. §112, first paragraph with respect to the scope of skeletal muscle relaxants. Further, claim 38 has been amended to call for the treatment to be administered to a human patient “experiencing a condition selected from the group consisting of migraine, cluster headache, muscle sprain, muscle spasm, spasticity, tension headache and tension related migraine.” Support for this language is found, e.g., in claim 38 as originally filed, as well as throughout the specification of the present application (see, for example, paragraphs 30, 32, 34, 36, 38, 41 and 42). Similar language is found in new independent claim 69.

**Claim Rejections – 35 U.S.C. §112**

In the Office Action, the Examiner rejected claims 38, 39, 41, 43, 45-52, 64 and 65 under 35 U.S.C. §112, first paragraph, the Examiner stating that the specification does not reasonably provide enablement for a method of treating migraines comprising the administration of a topical formulation comprising any skeletal muscle relaxant and/or any ergot alkaloid, without undue experimentation.

With respect to skeletal muscle relaxants, Applicant has amended the claims such that tizanidine is specified as the skeletal muscle relaxant. This change is made without prejudice and for the sole purpose of expediting prosecution of this application.

The Examiner's rejection based on non-enablement is respectfully traversed. As stated in the MPEP at §2164.08, the Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'." *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). In this regard, while the Examiner has stated that there is a general lack of predictability in the pharmaceutical art, citing *In re Fisher*, 427 F.2d 833 (CCPA 1970), the Applicant has provided ample information for a person having ordinary skill in the art, armed with the present specification, to test the specific classes of drugs claimed without undue experimentation, and determine, e.g., the effective dosage to be included in the unit dose which is applied according to the claimed methods of the invention.

The Examiner's attention is respectfully directed to the Examples provided in the present application, in which a skeletal muscle relaxant (tizanidine), an ergot alkaloid (methysergide) and a serotonin agonist (sumatriptan) and an ergot alkaloid (methysergide) were applied topically to humans in specified dosages with specified results. Examples 1-10, pages 36-42 of the specification. Furthermore, the Examiner has ignored the information contained in

the specification which provides guidance to those persons of ordinary skill in the art as to choices of skeletal muscle relaxants and dosages, as well as relative potencies of these agents. In this regard, the Examiner's attention is respectfully directed to pages 25-26 of the specification. Therein, at paragraph [0101], a list of centrally acting skeletal muscle relaxants which may be useful in the present invention is provided. At paragraph [0105], the dose of skeletal muscle relaxant is explained relative to the desired therapeutic effect. At paragraph [0106], detailed information is provided concerning useful dosages of the skeletal muscle relaxant tizanidine. At paragraph [0107], general dosages of skeletal muscle relaxants for use in the invention are provided. At paragraph [0108], comparative potencies of various skeletal muscle relaxants are provided. In the Examples, actual dosages of tizanidine used were reported.

Therefore, in summary, Applicant has provided examples of a skeletal muscle relaxant in use (tizanidine), examples of other potentially useful drugs in that class, potential dosages to be included in a unit dose and relative potencies of these drugs. That information is more than sufficient to provide enablement of the class of drugs. The class of agents is not limitless, and the Examiner's rejection seems to be based on the unrealistic and unreasonable expectation that Applicant test every single drug that Applicant wishes to encompass within the claims, despite the fact that there is clearly no requirement under U.S. law or under U.S. patent practice that Applicant provides such information.

Similarly, with respect to the ergot alkaloids (now included in the claims only in combination with the skeletal muscle relaxant, tizanidine), additional information is provided in the specification at pages 22-24. Specifically, at paragraph [0087], the general chemical structure of these agents is discussed; at paragraphs [0088] and [0089], specific examples of such drugs are provided; at paragraphs [0090] - [0092], further information is provided concerning ergotamine and dihydroergotamine, and dosages of the same; at paragraph [0093], information concerning methylsergide and dosages of the same are provided; at paragraph [0094], generalized dosages for the class of ergot alkaloids is provided; and in paragraph [0095],

information concerning the synthesis of this class of drugs is provided. Furthermore, Applicant has provided examples of treatment with methylsergide (see Examples).

Therefore, in summary, Applicant has provided examples of an ergot alkaloid in use (methylsergide), examples of other potentially useful drugs in that class, potential dosages to be included in a unit dose and relative potencies of these drugs. That information is more than sufficient to provide enablement of the class of drugs. The class of agents is not limitless, and the Examiner's rejection seems to be based on the unrealistic and unreasonable expectation that Applicant test every single drug that Applicant wishes to encompass within the claims, despite the fact that there is clearly no requirement under U.S. law or under U.S. patent practice that Applicant provides such information.

With respect to serotonin agonists, additional information is provided in the specification at page 24. Paragraph [0096] provides a list of serotonin agonists which may be useful in the invention, and paragraph [0097] provides dosages for sumatriptan. Applicant has also provided examples of a serotonin agonist in use (sumatriptan). Furthermore, the art itself is developed to the point where one skilled in the art knows and has guidance that others have administered indole serotonin agonists topically and therefore has an expectation that such administration is possible. For example, the Zelrix™ iontophoretic patch presently contemplated for commercialization by NuPathe, Inc., is the subject of recent press announcements and publications. The drug in this patch is sumatriptan. See Exhibit 1. Additionally, attached as Exhibit 2 to this Amendment is an Abstract of a publication concerning the use of zolmitriptan from an iontophoretic patch. Further, attached as Exhibit 3 to this Amendment is an Abstract of a publication concerning the use of another indole serotonin agonist, rizatriptan, through the skin as either a solution or in liposomes. Exhibits 1 and 2 were published in 2009 and Exhibit 3 in 2008, respectively, and therefore are submitted to show the knowledge base of those skilled in the art, rather than as prior art.

Further, submitted herewith is a copy of the Declaration of Inventor Dr. Ronald Aung-Din which was submitted during the prosecution of Applicant's U.S. Application Serial No. 11/999,093 (now abandoned). At paragraph 32 of his Declaration, the inventor states that he has further administered two other indole serotonin agonists, rizatriptan benzoate (derived from Maxalt®) and frovatriptan succinate (derived from Frova®) at doses of 1-2 mg and 0.5-1 mg respectively to migraine patients using the aqueous topical vehicle described in Examples 4 and 7 of that application (see Examples 7-9 of the present specification, which utilizes the same aqueous topical vehicle).

Furthermore, the art has recognized the class of drugs as being useful topically - see, e.g., U.S. Patent No. 5,807,571 (List), relied upon in an obviousness rejection of Applicant's U.S. Application Serial No. 11/999,093 (now abandoned). Given the information contained in the specification directing one skilled in the art regarding the particular class of agent and the range of dosing, along with the general knowledge of a person of ordinary skill in the art as reflected, e.g., by List, it would not cause undue experimentation for one skilled in the art to arrive at alternative serotonin agonists/dose combinations.

Simply put, there is more than sufficient evidence of enablement based on the specification of the present application, and based on the body of knowledge available to those skilled in the art. The claimed class of agents do not represent a "hunting license", but rather a well-known and defined class of active agents to those having ordinary skill in the art.

It is respectfully submitted that the Examiner's rejection has been overcome and should be removed.

In the Office Action, the Examiner rejected claim 56 because the claim recites the limitations active metabolites and prodrugs thereof. This rejection is moot in view of the cancellation of claim 56. Furthermore, similar limitations in pending claims 53 and 60 have been removed.

**Claim Rejections – 35 U.S.C. §103**

In the Office Action, the Examiner rejected claims 38, 39, 41, 43, 45-52, 56-58, 64 and 65 under 35 U.S.C. §103(a) as being unpatentable over Franz et al. GB 2098865 A in view of Saper et al. (2002, Headache, Volume 42, pages 470-482) and Aung-Din U.S. Publication No. 2003/0013753.

The Examiner's rejection is respectfully traversed.

Franz is directed to a topical pharmaceutical composition in the form of a microemulsion incorporating a skin-penetrable active agent. The active agent may be tizanidine, although the microemulsions are said to be indicated for the systemic administration "of any active agent." Page 4, lines 22-35. Franz does not hint or suggest that its formulations should be applied "onto the skin of a human patient at the posterior cervical area in close proximity to the brain stem" as required by the present claims. Indeed, Franz is not directed to a method of treatment at all, but rather to the skin penetration of active agents.

To the extent that Franz directs one of ordinary skill in the art at all, it would lead one away from the claimed method. In fact, at page 5, lines 46 – 54, Franz discusses permeation of human abdominal skin, and at page 6 lines 23-24, tizanidine was applied behind the ear.

Saper et al. describes a clinical study in which all patients treated with tizanidine were treated with tizanidine tablets orally to assess the efficacy of tizanidine as adjunctive ***prophylactic therapy*** for chronic daily headache (chronic migraine, migrainous headache, or tension-type headache).

In contrast to the presently claimed invention, Saper et al. seek to use tizanidine as adjunctive prophylactic therapy, ***not as a rapid treatment of a condition which is occurring at the time of treatment (acute treatment)***. In order to further clarify this difference, independent

claim 38 has been amended to call for the treatment to be applied to a human patient “experiencing a condition selected from the group consisting of migraine, cluster headache, muscle sprain, muscle spasm, spasticity, tension headache and tension related migraine... such that the unit dose provides a therapeutic effect within about 2 hours after topical administration to the human patient.” Thus, the presently claimed method is for acute treatment, whereas Saper et al. describes prophylactic therapy. These situations are not the same, nor does Saper et al. hint or suggest that (oral) tizanidine can be used, either alone or together with other active agents, to treat acute conditions.

The Examiner relies on Aung-Din as teaching formulations and methods of treating migraine with a serotonin agonist, and that the treatment is preferably accomplished via administration to the posterior cervical region of the human experiencing a migraine.

However, Aung-Din does not hint or suggest that tizanidine can be useful, either together with a serotonin agonist or alone, in acute treatment of migraine. Nor does Aung-Din hint or suggest any beneficial effects of any other drugs being administered at the posterior cervical region of a human patient.

In the Office Action, the Examiner admitted that there is a general lack of predictability in the pharmaceutical art, and stated that “it would be unpredictable for the skilled artisan to treat migraines with a topical formulation containing any skeletal muscle relaxant and/or any ergot alkaloid since the structures of each drug will vary and not all drugs are capable of being absorbed through the skin.” Office Action, page 5. Given the Examiner’s admission on the record of the Examiner’s view that there is lack of predictability even among agents in the same class of drugs, the Examiner’s rejection of the administration of tizanidine at the posterior cervical region of a human patient based on the use of a different drug in a completely different class of drugs is baseless and should be removed.

Indeed, absent the improper hindsight use of the present specification, there is nothing within the prior art suggesting the administration of a skeletal muscle relaxant such as tizanidine at the posterior cervical region of a patient for the acute treatment of “experiencing a condition selected from the group consisting of migraine, cluster headache, muscle sprain, muscle spasm, spasticity, tension headache and tension related migraine... such that the unit dose provides a therapeutic effect within about 2 hours after topical administration to the human patient.” In this regard, the Applicant has demonstrated the benefits of treatment (rapid onset of therapeutic effect) at the posterior cervical region of human patients with respect to tizanidine (see Examples 1 -5). The Examiner’s attention is further directed to the fact that the claims reflect the fact that the patient is experiencing, e.g., migraine at the time of treatment, and that the treatment provides a rapid therapeutic effect (e.g., within about 2 hours as set forth in claims 38 and 69; see also claim 73, which sets the time for effect at from about 5 to about 30 minutes).

Applicant has also demonstrated the benefits of treatment of serotonin agonists via administration of the same at the posterior cervical region of a patient for the acute treatment of migraine, as set forth, e.g., in the previously mentioned Declaration of the Inventor submitted herewith (originally submitted during the prosecution of Applicant’s U.S. Application Serial No. 11/999,093, now abandoned).

In this regard, the Examiner’s attention is respectfully further directed to dependent claims 39 and 60-63, dependent directly or indirectly from claim 38, and claims 69-72 and 75 which further require a therapeutically effective amount of a serotonin agonist. It is respectfully submitted that the combination of tizanidine and a serotonin agonist in the claimed method is patentable over the prior art of record. In this regard, the Examiner’s attention is respectfully directed to Exhibit 4 to this Amendment, which is a (non-prior art) publication previously made of record as Reference “FE” in Applicant’s IDS filed March 10, 2010 (Part 3 of 3). Likewise, claims 53-55 are dependent claims which further require the presence of a therapeutically effective amount of an ergot alkaloid. It is respectfully submitted that the combination of tizanidine and an ergot alkaloid in the claimed method is patentable over the prior art of record.

**Conclusion**

It is respectfully submitted that all of the Examiner's requirements have been met by the actions taken in this Amendment. However, the Examiner is invited to contact the undersigned by telephone if it is determined that any further issues remain.

A favorable action on the merits is respectfully requested.

Respectfully submitted,  
DAVIDSON, DAVIDSON & KAPPEL, LLC

By: /Clifford M. Davidson/  
Clifford M. Davidson  
Reg. No. 32,728

DAVIDSON, DAVIDSON & KAPPEL, LLC  
Patents, Trademarks and Copyrights  
485 Seventh Avenue, 14<sup>th</sup> Floor  
New York, New York 10018  
(212) 736-1940

## Exhibit 1 - Amendment for USSN 11/999,093

### Zelrix: a novel **transdermal** formulation of **sumatriptan**.

09-51 200919438727

NDN- 234-2224-4751-3

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Nat Lib of Medicine

#### **AUTHORS**

-

Pierce, Mark; Marbury, Thomas; O'Neill, Carol; Siegel, Steven; Du, Wei; Sebree, Terri

#### **JOURNAL NAME**

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#### **CORPORATE AUTHOR**

-

NuPathe-Research and Development, Conshohocken, PA 19428, USA.

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English

**OBJECTIVE:** This study evaluated the pharmacokinetic and tolerability profiles of Zelrix (NuPathe Inc., Conshohocken, PA, USA), the novel formulation of **sumatriptan** (formerly known as NP101). **BACKGROUND:** Migraine is an episodic headache disorder characterized by a combination of neurological, gastrointestinal, and autonomic symptoms. Gastrointestinal disturbances, including nausea, vomiting, and gastric stasis are common and can result in significant impact on treatment. Triptans are 5-hydroxytryptanimes (1B/1D) agonists that work on the trigeminal nerve that is activated during migraine. All triptans approved for use in the US are currently available as oral formulations; however, this may not be the ideal route of administration for many migraineurs. **Sumatriptan** is also available as a nasal spray and subcutaneous (s.c.) injection. Therefore, the need to develop improved methods for noninvasive parenteral delivery of triptans remains high. **METHODS:** This was a Phase I, single-center, open-label, crossover study that assessed the pharmacokinetic properties of a single dose of **sumatriptan** delivered using an iontophoretic **transdermal** patch in comparison with oral, injection, and nasal delivery. Subjects were healthy male and female volunteers who received each of 5 treatments: **sumatriptan** 100 mg oral tablets, **sumatriptan** 6 mg

s.c., sumatriptan 20 mg nasal spray, Zelrix I (transdermal patch with 3 g of gel solution delivering 6 mg of sumatriptan transdermally), or Zelrix II (transdermal patch containing 2.6 g of gel solution delivering 6 mg of sumatriptan). RESULTS: The C(max) for Zelrix was reduced to 30% and 28% of the sumatriptan s.c. dose, thereby reducing the risk of triptan-like sensations associated with high peak plasma concentrations. Plasma concentrations for Zelrix I and Zelrix II were intermediate between those for oral and nasal sumatriptan doses tested. Transdermal patch delivery of sumatriptan to the systemic circulation reached plasma concentrations of 10 ng/mL within about 30 minutes. The mean drug delivery of Zelrix I and II was 6.11 mg (confidence intervals CI 5.33-6.88) and 6.09 mg (CI 5.52-6.66), respectively. The AUC(0-inf) was approximately 99% for the Zelrix I patch and 100% for the Zelrix II patch as compared with sumatriptan 6 mg s.c. dose. Both doses of sumatriptan transdermal patches were well tolerated. Skin reactions at the patch site were mild and erythema resolved in most subjects within 48-72 hours. CONCLUSIONS: The results from this study show that sumatriptan administration using a novel iontophoretic transdermal technology delivers plasma levels within the range for nasal spray, tablet, and injectable sumatriptan. Zelrix I and II were well tolerated and adverse events were mild and transient. Transdermal delivery of sumatriptan using the SmartRelief iontophoretic technology may prove beneficial for a large segment of the migraine population based upon fast, consistent delivery of drug and avoidance of common gastrointestinal disturbances associated with migraine.

## Exhibit 2 - Amendment for USSN 11/999,093

### Controlled non-invasive **transdermal** iontophoretic delivery of **zolmitriptan** hydrochloride in vitro and in vivo

09-15 1402177  
NDN- 118-0149-4768-3

IPA

Thomson Scientific

#### **AUTHORS**

-

Patel, SR; Zhong, H; Sharma, A; Kalia, YN

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#### **AUTHOR AFFILIATION**

-

Univ Geneva, Med Chem Lab, 30 Quai Ernest Ansermet, CH-1211 Geneva 4, Switzerland

#### **EMAIL**

-

yogi.kalia@pharm.unige.ch

#### **PUBLICATION COUNTRY**

-

Netherlands

#### **LANGUAGE**

English

The objective was to investigate the **transdermal** delivery kinetics of **zolmitriptan** from an iontophoretic patch system in Yorkshire swine in vivo. Preliminary in vitro experiments showed that cumulative drug transport during a 6-h current application ( $0.25 \text{ mA cm}^{-2}$ ) was independent of patch load ( $263.7 \pm 92.7$ ,  $357.2 \pm 85.9$ ,  $374.9 \pm 74.3$  and  $335.9 \pm 27.7 \text{ mug cm}^{-2}$  for 7.5, 15, 45 and 90 mg patch loads, respectively; ANOVA.  $p < 0.05$ ); the steady-state flux was similar to  $92 \text{ mug cm}^{-2} \text{ h}^{-1}$ . The in vivo studies used multistep current profiles to demonstrate (i) rapid drug uptake and (ii) the effect of superposing a bolus input on basal drug levels. In both studies, **zolmitriptan** was detected in the blood after 2.5 min; drug levels were  $7.1 \pm 1.7$  and  $10.4 \pm 3.5 \text{ ng ml}^{-1}$  at  $t = 30 \text{ min}$  in Studies 1 and 2, respectively. In Study 2, increasing current intensity from 0.2 to 1.4 mA ( $0.05$ - $0.35 \text{ mA cm}^{-2}$ ) at  $t = 180 \text{ min}$  caused **zolmitriptan** levels to rise from  $9.38 \pm 0.93 \text{ ng ml}^{-1}$  at  $t = 180 \text{ min}$  to  $13.57 \pm 1.85 \text{ ng ml}^{-1}$  at  $t = 190 \text{ min}$ ; a similar to 50% increase in 10 min. Extrapolation of these results to humans suggests the feasibility of delivering therapeutic amounts of **zolmitriptan** at faster rates than those from existing dosage forms. (C) 2008 Elsevier B.V. All rights reserved.

### Exhibit 3 - Amendment for USSN 11/999,093

#### Elastic liposomal formulation for sustained delivery of antimigraine drug: In vitro characterization and biological evaluation

08-23 1387303  
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IPA

Thomson Scientific

#### **AUTHORS**

Garg, T; Jain, S; Singh, HP; Sharma, A; Tiwary, AK

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#### **AUTHOR AFFILIATION**

Punjab Univ, Dept Pharmaceut Sci & Drug Res, Patiala 147002, Punjab, India

#### **EMAIL**

subheetjain@rediffmail.com

#### **PUBLICATION COUNTRY**

USA

#### **LANGUAGE**

English

The aim of this study was to prepare and characterize a **topical** formulation for sustained delivery of **rizatriptan**. Elastic liposomal formulation of **rizatriptan** was prepared and characterized for different characteristics by evaluating in vitro and in vivo parameters. The in vivo performance of optimized formulation was evaluated for antimigraine activity in mice using morphine withdrawal-induced hyperalgesia. The in vitro skin permeation study across rat skin suggested carrier-mediated **transdermal** permeation for different elastic liposomal formulation to range between  $18.1 \pm 0.6$  and  $42.7 \pm 2.3$   $\mu\text{g}/\text{h}/\text{cm}^2$ , which was approximately 8-19 times higher than that obtained using drug solution. The amount of drug deposited was 10-fold higher for elastic liposome ( $39.9 \pm 3.2\%$ ) than using drug solution ( $3.8 \pm 1\%$ ); similarly the biological activity of optimized elastic liposome formulation was found to be threefold higher than the drug solution. On the basis of the results, it can be concluded that the elastic liposomal formulation provided sustained action of **rizatriptan** due to depot formation in the deeper layer of skin.

# HEADACHE

The Journal of Head and Face Pain

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**Program Abstracts**  
**46th Annual Scientific Meeting**  
**American Headache Society**  
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# Topical Tizanidine (Zanaflex®) Gel Effective in Migraine and Tension-Type Headache

Ronald Aung-Din, M.D. and Fred Kinnard, R.Ph.

## INTRODUCTION

Migraine and tension-type headache may have symptoms of cervical muscle tightness and associated localized pain. These symptoms may be attributable to the trigeminal caudal nucleus with involvement of the upper cervical roots. Alternatively, migraines with concomitant cervical spondylosis may trigger migraine attacks with exacerbations of their cervical condition. Oral muscle relaxants with concomitant steroid and botulinum toxin have been used in treating headache associated with significant muscle spasm. The drawback with oral muscle relaxants is primarily in their central nervous system suppressant effects of lethargy, drowsiness and fatigue. These side effects may contraindicate their use. Benzodiazepines may be habit-forming, create tolerance and prone to withdrawal symptoms such as seizures. Tizanidine is an oral alpha-2-adrenergic agonist with myotonolytic activity, which has been used in treating migraine and tension-type headache.

## OBJECTIVES

A single-dose open pilot study was undertaken in 52 patients to determine the efficacy of tizanidine topically applied to the posterior cervical muscles in relieving an acute headache episode in relieving pain and migraine symptoms.

## METHODS

### Design

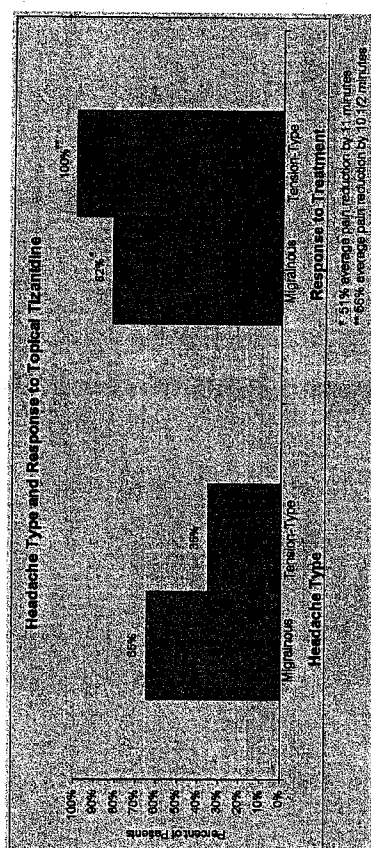
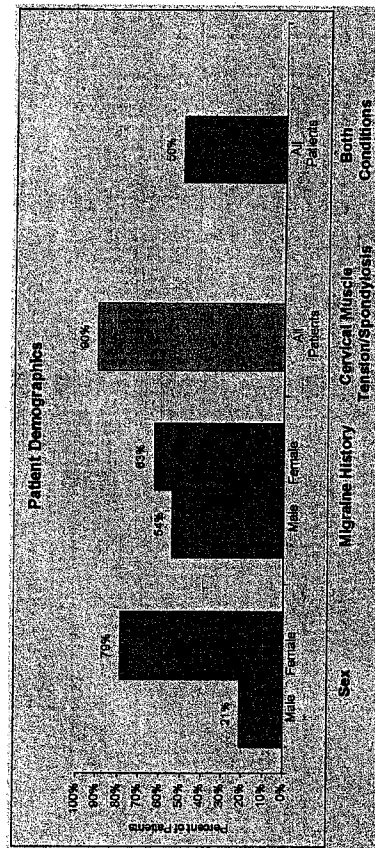
- Open-label, single-dose, prospective study (N=52)
- Subjects: adult male and female patients with migraine and tension type headaches
- Headache intensity ranged from mild to severe with most in the moderate to severe category.

### Treatment

- Patients treated in the clinic for a headache episode with transdermal tizanidine gel compounded in the dermat-potentiating compounding agent Lipoderm®. It's concentration of 2mg/ml.
- 1 mg compounded tizanidine gel in a tuberculin syringe was applied and rubbed into the posterior cervical muscles on the side of the headache. With bilateral head pain, the dose was split between the two sides.

### Assessments

- Patients asked to characterize a) headache type: migrainous (throbbing head pain, photophobia, nausea, and vomiting) or tension (bilateral head pain, neck stiffness, and occipital or parietal tenderness); b) intensity of headache prior to treatment, 0 to 10; c) time to reduction of headache pain by at least 50%; d) side effects.



## RESULTS

### Demographics

- 41 females and 11 males participated in the study
- Mean age of participants: 45 years
- Prior history of migraine in 32 patients (61%); 26 females and 6 males
- Mean duration of migraine headaches: 19 years for females and 14 years for males
- History of cervical muscle tension or cervical spondylosis in 47 patients (90%)
- History of both migraine and cervical tension in 26 patients (50%)

### Outcome

- Both types of headache were relieved with topical tizanidine gel (migrainous 82%, muscle tension type 100%)
- Reduction in cervical muscle tension with improved range of motion was noted in all treated patients
- Patients with migrainous headache experienced reduction in light/sound sensitivity and nausea in addition to head pain relief
- Adverse events included transient sensation of warm feeling at the application site, slight lightheadedness and euphoria. There were no serious side effects and no significant lethargy, drowsiness or fatigue

## CONCLUSIONS

- This pilot study suggests transdermal tizanidine applied to the posterior cervical region may be effective for migraine and tension type headache
- Three prior studies (IHC 2001, AHS 2002, and AHS 2003) suggested the efficacy of transdermal tizanidine. There may exist a place for combination tizanidine and topical steroid therapy, nullifying the systemic side effect potential of these drugs. A synergistic effect from different mechanisms of action may be potentially evoked.
- Further studies including placebo controlled design are necessary to confirm these preliminary findings of this novel dosage form of acute headache therapy.

## CONTACT INFORMATION

Ronald Aung-Din, MD  
11111 North Central Expressway, Suite 200  
Bartonsville, FL 32020  
Phone: 941-851-2860  
Fax: 941-365-3168

**Objectives:** To describe the response to extended release divalproex sodium in a patient with retinal migraine.

**Background:** Retinal migraine is an uncommon headache characterized as repeated attacks of monocular visual loss lasting less than sixty minutes and associated with headache. Prior detailed information regarding the pathophysiology of the monocular visual loss implicates possible vasospasm of the retinal vasculature. Treatment typically consists of prophylactic calcium channel antagonists, such as verapamil.

**Methods:** This fifty-year-old right-hand dominant male presented to the outpatient clinical setting with a new onset of repeated right monocular visual loss associated with headache over the past several months. This patient has a history of severe debilitating throbbing quality headaches associated with nausea and photophobia since the age of the early forties. The headaches typically were unassociated with a preceding aura. The visual scotoma of the right eye begins in the temporal hemifield, which progressively spreads across to the nasal hemifield, until complete loss has occurred. The patient has performed the cover-uncover test to clearly delineate the monocular loss of vision in the right eye alone. The visual loss lasts an average of 30 minutes with complete resolution, followed shortly thereafter by a headache. Bright light is often a trigger to the symptoms. The visual symptoms with headache typically occur twice weekly. Ophthalmologists have previously evaluated the patient's ocular fundus both with and without the visual loss, with no abnormalities documented. Magnetic resonance imaging of the brain and the cerebral vasculature did not reveal any abnormalities. The patient has no significant medical history and laboratory investigations were normal.

**Results:** The patient's headache met the International Headache Society criteria for retinal migraine. The patient was initially started on verapamil 240 milligrams (mg) daily in divided doses. The response was poor and the dose was titrated upwards to 360 mg daily in divided doses, but was discontinued secondary to intolerable side effects. Divalproex sodium extended release was then initiated at 500 mg nightly. Upon follow-up, the patient reported a rare occurrence of the visual symptoms and a significant decline in headache frequency.

**Conclusions:** Retinal migraine is an uncommon headache often treated with prophylactic calcium channel antagonists as the underlying pathology is thought to be due to retinal vasospasm. The patient's dramatic response to divalproex sodium suggests the possibility of more than one mechanism as a cause to the visual symptoms, such as neuronal spreading depression. The use of divalproex sodium may be a potential alternative treatment. Further investigation is necessary.

#### S126

#### Topical Tizanidine (Zanaflex) Gel Effective in Migraine and Tension-Type Headache

Aung-Din R.; Kinnard F.

Neurology, Ronald Aung-Din MD PA, Sarasota, FL

**Objectives:** A single-dose open pilot study was undertaken in 52 patients to determine the efficacy of tizanidine topically applied to the posterior cervical muscles during an acute headache episode in relieving pain and migraine symptoms.

**Background:** Migraine and tension-type headache may have symptoms of cervical muscle tightness and associated localized pain. These symptoms may be attributable to the trigeminal caudal nucleus with involvement of the upper cervical roots. Alternatively, migraineurs with concomitant cervical spondylosis may trigger migraine attacks with exacerbations of their cervical condition.

Oral muscle relaxants and injections of steroid and botulinum toxin have been used in treating headache associated with signif-

icant muscle spasm. The drawback with oral muscle relaxants is primarily in their central nervous system suppressant effects of lethargy, drowsiness and fatigue. These side effects may contraindicate their use. Benzodiazepines may be habit-forming, create tolerance and prone to withdrawal symptoms such as seizures. Tizanidine is an oral alpha-adrenergic agonist with myotonolytic activity, which has been used in treating migraine and tension-type headache.

**Methods:** Of the 52 patients, 60% (31/52) had prior diagnosis of migraine. 90% (47/52) had history of cervical tension or spondylosis; 50% (26/52) had both. Of treated headaches, 65% were migrainous with symptoms of throbbing head pain, photophobia, sonophobia and nausea. The remaining headaches (35%) were primarily muscle tension in nature involving the posterior cervical, occipital or temporalis muscles.

Tizanidine 2mg/ml, was compounded in the dermal penetrating agent LipoDerm. 1 mg compounded tizanidine gel in a tuberculin syringe was applied and gently rubbed into the posterior cervical muscles on the side of the headache. With bilateral head pain, the dose was split between the two sides. Headache intensity ranged from mild to severe with most in the moderate to severe category.

**Results:** Both types of headache were relieved with tizanidine gel. Reduction in cervical muscle tension with improved range of motion was noted in all patients. Patients with migraine experienced reduction in light and sound sensitivity and nausea in addition to head pain alleviation. Those with primarily muscle tension head pain experienced the most relief from the transdermal tizanidine (100% vs. 82%). Adverse events included a transient sensation of a "warm feeling" in the application area, slight light-headedness and euphoria. There were no serious side effects. There was no significant lethargy, drowsiness or fatigue.

**Conclusions:** Transdermal tizanidine applied to the posterior cervical region may be effective for migraine and tension-type headache. Three prior studies (IHC 2001, AHS 2002 and AHS 2003) suggested the efficacy of transdermal sumatriptan. There may exist a place for combination triptan/tizanidine transdermal therapy, nullifying the systemic side effect potential of these drugs. A synergistic effect from different mechanisms of action may be potentially evoked. Controlled studies are necessary to confirm the above preliminary findings.

#### S127

#### Dystonia and Headaches: The Response to Botulinum Toxin Type A Therapy

Ondo W.G.<sup>1</sup>; Galvez-Jimenez N.<sup>2</sup>; Gollomp S.M.<sup>3</sup>

<sup>1</sup>Parkinson's Disease Center and Movement Disorders Clinic,

Houston, TX; <sup>2</sup>The Cleveland Clinic Florida, Weston, FL;

<sup>3</sup>Lankenau Hospital, Wynnewood, PA

**Objectives:** To determine the response to botulinum toxin type A (BoNT-A) treatment in patients with cervical dystonia and associated headache.

**Background:** Section 11.2.3 of the revised International Headache Society classification of headaches identifies headache associated with craniocervical dystonia. Headaches and disability associated with cervical dystonia (CD) may respond to BoNT-A treatment.

**Methods:** This 12-week, open-label, prospective study evaluated the efficacy of BoNT-A for headache and dystonia in patients diagnosed with cervical dystonia. Following BoNT-A injections at the baseline visit, patients were assessed at 4, 8, and 12 weeks for changes in headache symptoms and HIT-6 scores measured quality of life. All patients maintained daily headache diaries. The Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) was measured at baseline, 4 weeks, and 12 weeks and